PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received three reviews from its previous journal but only two reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Enhancing the Public Health Impact of Latent Tuberculosis Infection Diagnosis and Treatment (ACT4): Protocol for a cluster randomized trial
AUTHORS	Oxlade, Olivia; Trajman, Anete; Benedetti, Andrea; Adjobimey, Menonli; Cook, Victoria; Fisher, Dina; Fox, Gregory; Fregonese, Federica; Hadisoemarto, Panji; Hill, Philip; Johnston, James; Long, R.; Obeng, Joseph; Ruslami, Rovina; Valiquette, Chantal; Menzies, Dick

VERSION 1 – REVIEW

REVIEWER	Dr Heinke Kunst Queen Mary University, London, UK
REVIEW RETURNED	29-Sep-2018

GENERAL COMMENTS	1. Enhancing the Public Health Impact of Latent Tuberculosis Infection Diagnosis and Treatment is an important study and will aid to to increase uptake of LTBI screening and treatment by public health interventions especially in high TB incidence countries. 2. The primary outcome is treatment initiation. Could the authors define treatment initiation further eg the patient has attended the TB clinic for treatment initiation, the TB doctor has issued a prescription or the HHC has been given the medication and has taken the first dose of LTBI treatment. 3. The length of LTBI treatment may be of importance for treatment initiation eg a HHC is more likely to accept treatment for a three months regimen compared to a 9 months regimen which should be taken into account in the final analysis. 4. Could the authors include what educational material was used at each, eg leaflets, posters etc. 5. Do all the sites have access to interpreters when conducting LTBI assessment and initiating treatment? Language barriers are often an important factor for drop-out in the LTBI cascade.

REVIEWER	Robert Belknap Director, Denver Metro TB Program Denver Health and Hospital Authority USA
REVIEW RETURNED	05-Nov-2018

GENERAL COMMENTS	This is an important study that will help guide interventions to improve TB prevention across a wide spectrum of countries with low, intermediate and high TB burden. The introduction mentions a pilot study conducted in Brazil. The protocol does not include any results of the pilot or state if those results will be published or made available. Since the interventions are expected to be locally specific and the main study does not include any countries in South America, I would encourage the authors to include the pilot results in an appendix to the main manuscript or publish them separately.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

2. The primary outcome is treatment initiation. Could the authors define treatment initiation further eg the patient has attended the TB clinic for treatment initiation, the TB doctor has issued a prescription or the HHC has been given the medication and has taken the first dose of LTBI treatment.

The following definition of treatment initiation was outlined in the study's Standard Operating Procedures:

…to estimate the number of patients starting LTBI therapy in ALL clinics (control and intervention clinics) starting from the beginning of Phase 1, we will rely on pharmacy records and/or written prescriptions in all sites. In many countries (and some of the Canadian provinces) the TB control program carefully controls access to all TB medications. In these countries patients receiving LTBI therapy will usually receive their TB medications at the designated TB treatment facility. These facilities dispense all TB medications to patients. In these settings the health providers who decide on LTBI therapy will directly dispense TB medications, or the household contacts go to a pharmacy within the same facility. In these settings, we only need pharmacy records regarding patients to whom treatment was dispensed. The health care personnel involved in dispensing TB medications may or may not be the same personnel who are involved in the evaluation and education of the household contacts. If the pharmacy is a separate unit within the health facility it will be easy to measure patients who start therapy carefully, while also avoiding any Hawthorne effect, because the pharmacy personnel will not be the same as the health care providers for the LTBI clinical services.

In order to clarify this important detail we have added the following information to the text in Line 188:

"In all sites treatment initiation for HHC will be defined as clinical or pharmacy records indicating that a prescription has been issued or, in clinics were medications are given directly to patients, a HHC being issued LTBI medication by a health care worker.."

3. The length of LTBI treatment may be of importance for treatment initiation eg a HHC is more likely to accept treatment for a three months regimen compared to a 9 months regimen which should be taken into account in the final analysis.

Thank you for this comment. Indeed, it is possible that patients may be more agreeable to starting a shorter treatment regimen. In all Canadian sites 4RIF is the standard regimen given to patients, while in the low middle income country (LMIC) sites all sites will use 6INH. At the analysis stage we will stratify by LMIC and Canadian sites in order to adjust for potential between country differences such as treatment duration. This detail has been clarified in the analysis section in Line 403. The additional text is shown below:

"We will also stratify findings by LMIC and Canadian sites in order to adjust for potential between country differences such as treatment duration…. "

4. Could the authors include what educational material was used at each, eg leaflets, posters etc.

Educational material is an example of a solution that sites may decide to adopt to strengthen their LTBI program. The specific approach to developing material will depend on the needs of the site. They may decide to create pamphlets, leaflets, flip charts, videos etc… The specifics will not be decided until the site has completed Phase 2 of the study. We therefore cannot elaborate on this point until the study is finished, at which point all details will be included in the main study publication. One additional detail- we have also requested that sites share all of the material that is developed so that it can be made publicly available to others who may be interested.

5. Do all the sites have access to interpreters when conducting LTBI assessment and initiating treatment? Language barriers are often an important factor for drop-out in the LTBI cascade.

Availability of interpreters will be determined by the level of routine care at the site. In the LMIC settings it would be rare that they would be made available as clinical staff usually speak the primary language of the site. In the Canadian sites routine care would generally include providing translators for the foreign born population where it was required. If however during their phase 1 evaluation sites identified language as a barrier for patients, they may opt to include translation as a "solution" to implement in Phase 2. They may also choose to generate patient material in multiple languages to better suit the needs of their patient population. In this case it would be part of the intervention provided in the trial.

Reviewer: 2

Please leave your comments for the authors below This is an important study that will help guide interventions to improve TB prevention across a wide spectrum of countries with low, intermediate and high TB burden. The introduction mentions a pilot study conducted in Brazil. The protocol does not include any results of the pilot or state if those results will be published or made available. Since the interventions are expected to be locally specific and the main study does not include any countries in South America, I would encourage the authors to include the pilot results in an appendix to the main manuscript or publish them separately.

The results of the pilot study in Brazil have been written up in a separate manuscript that will be submitted for publication shortly. This information has been added to the main text in line 132 as follows:

"Results from the Brazil pilot will be published as a separate manuscript."

Additional comment from Authors:

We have also added a few more details to the section on Economic Analysis in lines 218, 412 and 425.

VERSION 2 – REVIEW

REVIEWER	Dr Heinke Kunst Queen Mary University, UK
REVIEW RETURNED	16-Jan-2019

GENERAL COMMENTS	I have previously reviewed the manuscript and have no further comments